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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,950	09/08/2006	**Helen Francis-Lang**	05-967-D5	5893

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,950	FRANCIS-LANG ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-15 and 20-25* is/are pending in the application.

4a) Of the above claim(s) *4,5,7,13-15 and 20-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 8-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/13/10 has been entered.

Claims 1-11, 13-15, and 20-25 remain pending. Claims 4, 5, 7, 13-15, and 20-25 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/27/09.

Claims 1-3, 6, and 8-11 are under consideration.

Rejections not reiterated are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6, and 8-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6, and 8-11 recite "the beta catenin pathway" in step (e) without proper antecedent basis. Those of skill in the art appreciate that beta-catenin is involved in a network of signal transduction pathways, not just a single pathway. For example, beta-catenin is involved in signaling involving Wnt, Akt/protein kinase B, epidermal growth factor (EGF), insulin-like growth factor, integrin-linked kinase, nuclear factor-κB, p53, Pin1, PTEN, FP(B) prostanoid receptor, nuclear hormone receptors such as peroxisome proliferator-activated receptors (PPARs), androgen receptor (AR) and retinoic acid receptor (RAR), and oxidative stress. Thus one of skill in the art would not know to which pathway the claims refer.

Claims 1-3, 6, and 8-11 require the step of "measuring the beta catenin pathway", which renders the claims indefinite. The claims are incomplete because they do not make clear how the pathway is to be measured. A metabolic pathway is a series of reactions that provide measurable outcomes, but it is not clear how one measures an entire pathway, or what is intended by "measuring the beta catenin pathway".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murray et al (J. Biol. Chem 272(44): 27521-27524, 1997).

Murray examined the role of PKC iota in drug-induced apoptosis in K562 cells, which normally display some resistance to drug-induced apoptosis. Murray first established that K562 cells expressed PKC iota, and then stably transfected K562s with a construct expressing antisense directed against PKC iota. This cell ine underexpressed PKC iota. Murray also made another K562 line that overexpressed PKC iota by stably transfecting K562s with a PKC iota expression vector. See abstract; and page 27522, Figs. 1 and 2, and right column, first full paragraph. Murray then treated each of these cell lines with drugs that induce apoptosis, i.e. okadaic acid and taxol. Murray found that K562 cells that overexpress PKC iota had an enhanced resistance to drug-induced apoptosis, whereas cells that underexpressed PKC iota were more susceptible to drug-induced apoptosis. Murray assayed apoptosis by examining DNA fragmentation and nuclear morphology. See Fig. 4 on page 27523.

Based on the results of Murray, one of ordinary skill in the art at the time of the invention would have predicted that inhibition of PKC iota expression in the cell line that overexpressed PKC iota would decrease the resistance to drug-induced apoptosis observed in that cell line, and would have been motivated to perform such an experiment in order to further confirm the role of PKC iota in drug-induced apoptosis. It would have been obvious for one of ordinary skill to use the antisense expression vector to inhibit PKC iota in the cell line in which PKC iota was overexpressed.

In summary, Murray provided a first system in which the effect of antisense against PKC iota was measured by northern blot. In this system, Murray contacted the cells with a PKC iota antisense and measured the expression of PKC iota in the

presence and absence of the antisense, detecting a change in PKC iota expression (see e.g. Fig. 2 on page 27522, and page 27522, right column, first full paragraph). Thus Murray anticipated claimed method steps (a)-(d). Note that the step of "identifying a beta catenin modulating agent" is inherent in the active steps carried out by Murray, i.e. in detecting a change in PKC expression.

Murray further provided a second assay system in which the cells overexpressed PKC iota. As discussed above, it would have been obvious to contact that system with the same PKC iota antisense used to make the first system, and to assess the effect on drug-induced apoptosis. In so doing, one would practice steps (f)-(h) of claims 1, 2, 6, 8, and 9. The limitation of "measuring the beta catenin pathway" in step (g) is considered to be met by Murray's assays of apoptosis. This is because beta catenin is known to be involved in the induction of apoptosis, thus all steps downstream of beta catenin in this process, including the DNA fragmentation nuclear morphological changes assayed by Murray, are considered to be part of "the beta catenin pathway". Assessment of these phenomena satisfies the the limitaitons of instant method step (g). Thus the invention as a whole was prima facie obvious.

Claims 1, 2, 6, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cowsert et al (US 20040014049) and Murray et al (J. Biol. Chem 272(44): 27521-27524, 1997).

Cowsert taught methods of inhibiting the expression of PKC iota in cultured cells by contacting the cells with an antisense oligonucleotide directed against PKC iota

mRNA. Cowsert indicated that a preferred target region of an mRNA may be employed in screening candidate antisense compounds. Candidate antisense compounds are those that inhibit the expression of a nucleic acid molecule encoding protein kinase C-iota. A screening method comprises the steps of contacting a preferred target region of a nucleic acid molecule encoding protein kinase C-iota with one or more candidate antisense compounds, and selecting for one or more candidate antisense compounds which inhibit the expression of a nucleic acid molecule encoding protein kinase C-iota. See paragraph 248. Cowsert exemplified screening in T-24 cells and A549 cells (see paragraph 281 and Tables 1 and 2, comparing PKC iota expression in the presence and absence of candidate antisense compounds. Thus Cowsert taught steps (a)-(d) of claims 1, 2, 6, and 8-10.

Once it is shown that the candidate antisense compound or compounds are capable of inhibiting the expression of a nucleic acid molecule encoding protein kinase C-iota, the candidate antisense compound may be employed in accordance with the invention. For example, Cowsert taught at paragraph 35 that expression patterns within cells or tissues treated with one or more antisense compounds are compared to control cells or tissues not treated with antisense compounds and the patterns produced are analyzed for differential levels of gene expression as they pertain, for example, to disease association, signaling pathway, cellular localization, expression level, size, structure or function of the genes examined. These analyses can be performed on stimulated or unstimulated cells and in the presence or absence of other compounds which affect expression patterns.

So, while Cowsert taught instant method steps (a)-(d) in generating antisense oligonucleotides that inhibit PKC iota expression, and suggested further use of these oligonucleoitdes in studying PKC iota function in a variety of settings, Cowsert did not explicitly teach instant method steps (e)-(g).

Murray investigated the role of PKC iota in the resistance to drug-induced apoptosis in K562 cells. As discussed above, Murray did so by establishing cell lines that either overexpressed or under expressed PKC iota, and then assayed drug-induced apoptosis in each of these lines.

In view of the teachings of both Cowsert and Murray, it was clear to those of ordinary skill in the art at the time of the invention that PKC-iota gene expression could be inhibited through the use of either antisense oligonucleotides or antisense expression vectors, and one would have understood that these were alternative approaches to achieving the same result. Accordingly the decision to use one approach or the other is simply a matter of design choice, and it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the antisense oligonucleotides of Cowsert to down-regulate PKC-iota expression in K562 cells instead of making a cell line that expresses PKC iota antisense. In doing so one of ordinary skill would have measured drug-induced apoptosis in the presence and absence of the oligonucleotides of Cowsert. This procedure would have met the limitations of instant steps (e)-(g) because the K562 cells represent a second assay system in which the oligonucleotides of Cowsert were used. The limitation of "measuring the beta catenin pathway" in instant step (g) is considered to be met by assaying apoptosis, as

discussed in the previous rejection. Thus the invention as a whole was prima facie obvious.

It is also noted that the combined references render the claimed method obvious in a second way, as follows. As discussed in the previous rejection Murray rendered obvious an experiment in which the effect of PKC iota on drug-induced apoptosis is confirmed by using antisense to knock down expression of PKC-iota in cells that overexpress PKC iota, and which have enhanced resistance to drug-induced apoptosis.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use any of the oligonucleotides of Cowsert to knock down expression of PKC iota in the cell line of Murray which overexpresses PKC iota, and to measure drug-induced apoptosis in the antisense-treated cells relative to that observed in identical untreated cells. It would have been obvious to use the oligonucleotides of Cowsert for this purpose because Cowsert taught that the oligonucleotides should be used to assess the effects of PKC iota expression on various cellular processes (see paragraph 35). The limitation of “measuring the beta catenin pathway" in instant step (g) is considered to be met by assaying apoptosis, as discussed above. Thus the active steps (f)-(h) of claims 1, 2, 6, and 8-9, and invention as a whole, were prima facie obvious.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cowsert et al (US 20040014049) and Murray et al (J. Biol. Chem 272(44): 27521-27524, 1997)

as applied to claims as 1, 2, 6, 8, and 9 above, and further in view of Summerton et al (Antisense & Nucleic acid Drug Dev. 7: 187-195, 1997).

The teachings of Cowsert and Murray are discussed at length above, and can be combined to render obvious method steps (a)-(g) of claims 1, 2, 6, 8, and 9 by using antisense oligonucleotides as an agent to inhibit PKC iota expression.

Neither Murray nor Cowsert taught morpholino phophorodiamidate antisense oligomers as required by instant claim 10.

Summerton taught that phosphorodiamidate morpholino (PMO) oligonucleotides overcome problems associated with first generation antisense chemistries, provide high and predictable activity in cells, and exhibit little or no non-antisense activity, afford good water solubility, are immune to nucleases. See abstract. Therefore one of ordinary skill in the art at the time of the invention would have found it obvious and would have been motivated to substitute PMO oligonucleotides for the oligonucleotide chemistry of Cowsert, in order to obtain the perceived advantages of PMO oligonucleotides. Thus the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's acting supervisor, Heather Calamita, can be reached at (571) 272-2876. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Richard Schnizer/
Primary Examiner, Art Unit 1635